HFD-615

OCT 1 5 1998

NDA 16-793/S-059

Pharmacia & Upjohn Company
7000 Portage Road
Kalamazoo, Michigan 49001

Attention: Rebecca K. Tong, M.S.
Regulatory Manager, U.S. Regulatory Affairs

Dear Ms. Tong:

Please refer to your supplemental new drug application dated March 5, 1998, received March 6, 1998, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for CYTOSAR-U (sterile cytarabine, USP) sterile powder.

The User Fee goal date for this application is September 6, 1998.

The supplemental application was submitted as a "Special Supplement-Changes Being Effected" under 21 CFR 314.70(c)(2)(i) and provides for a revised package insert with the following changes:

1. PRECAUTIONS: (a) A third reference (Smith et al, 1997; reference 49) was added to support the precautionary statement regarding CNS toxicity in patients with renal impairment. (b) A statement about the possibility of acute pancreatitis being schedule dependent was added (McBride et al, 1996; reference 50).

2. ADVERSE REACTIONS: Pancreatitis is added to the list of less frequent adverse reactions.

3. REFERENCES: The references described above [49 and 50] were added to the list. The references supporting these changes are provided in Attachment C.

We have completed the review of this supplemental application and it is approved. However, the following changes should be completed at the next printing or within 90 days, whichever comes first.

1. Please modify the trade dress so that For Intravenous, Intrathecal and Subcutaneous Use Only is directly below established name and not separated by the bar.

2. REFERENCES section should be revised to delete all references except for the references that refer to safe handling procedures (see below for updated listings). The superscripts in the text should also be revised to reflect these changes.

REFERENCES

1. Recommendations for the Safe Handling of Parenteral Antineoplastic Drugs, NIH Publication No. 83-2621. For sale by the Superintendent of Documents, U.S. Government Printing office, Washington, DC 20402.

2. AMA Council Report, Guidelines for Handling Parenteral Antineoplastics. JAMA, 1985; 2.53(11):1590-1592.

3. National Study Commission on Cytotoxic Exposure - Recommendations for Handling Cytotoxic Agents. Available from Louis P. Jeffrey, ScD., Chairman, National Study Commission on Cytotoxic Exposure, Massachusetts College of Pharmacy and Allied Health Sciences, 179 Longwood Avenue, Boston, Massachusetts 02115.

4. Clinical Oncological Society of Australia, Guidelines and Recommendations for Safe Handling of Antineoplastic Agents. Med J Australia, 1983; 1:426-428.

5. Jones RB, et al: Safe Handling Of Chemotherapeutic Agents: A Report from the Mount Sinai Medical Center. CA - A Cancer Journal for Clinicians, 1983; (Sept/Oct) 258-263.

6. American Society of Hospital Pharmacists Technical Assistance Bulletin on Handling Cytotoxic and Hazardous Drugs. Am J. Hosp Pharm, 1990; 47:1033-1049.

7. Controlling Occupational Exposure to Hazardous Drugs. (OSHA Work-Practice Guidelines), Am J Health-Syst Pharm, 1996; 53:1669-1685.

3. Storage Conditions on the carton labels for drug product should be revised to read:

Store at 25° (77°F); excursions permitted to 15°-30°C (59°-86°F)
[See USP Controlled Room Temperature]

4. Storage statement in the HOW SUPPLIED section in the pi should be revised to read:

Store at 25°C (77°F); excursions permitted to 15°-30°C (59°-86°F)
[See USP Controlled Room Temperature]

5. The statement of "Caution: Federal law prohibits.. .." should be revised to read:

   "Rx only" or "℞ only" symbols on drug product labels.

6. Under Cell *Culture Studies:* delete second paragraph regarding antiviral effects.

7. Delete entire *Animal Studies* section.

8. Under Use *in Pregnancy,* replace "(See ANIMAL TOXICOLOGY") with "Cytarabine causes abnormal cerebellar development in the neonatal hamster and is teratogenic to the rat fetus." Delete fourth sentence- "If CYTOSAR-U is used.. ..".

9. Delete entire *Animal Toxicology* section (at end).

10. Under PRECAUTIONS Section, delete the proposed sentence "There is evidence that this may be schedule dependent."

11. Under PRECAUTIONS Section, replace the sentence: "Acute pancreatitis has been reported . . . ." with the following sentence: "Acute pancreatitis has been reported to occur in a patient receiving Cytosar-U by continuous infusion and in patients being treated with Cytosar-U who have had prior treatment with L-asparaginase."

Should a letter communicating important information about this drug product (i.e., a Dear Doctor letter) be issued to physicians and others responsible for patient care, we request that you submit a copy of the letter to this NDA and a copy to the following address:

MEDWATCH, HF-2
FDA
5600 Fishers Lane
Rockville. MD 20852-9787

We remind you that you must comply with the requirements for an approved NDA set forth under 21 CFR 314.80 and 314.81.

If you have any questions, please contact Patrick Guinn, Project Manager, at (301) 827-1537.

Sincerely yours,

Robert L Justice, M.D 10/9/98

Robert L. Justice, M.D.
Acting Director
Division of Oncology Drug Products
Office of Drug Evaluation I
Center for Drug Evaluation and Research

Enclosure